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| <b>Section:</b>    | Prescription Drugs     | <b>Effective Date:</b>       | July 1, 2026      |
| <b>Subsection:</b> | Miscellaneous Products | <b>Original Policy Date:</b> | September 9, 2022 |
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**Last Review Date:** June 11, 2026

## Zynteglo

### Description

#### Zynteglo (betibeglogene autotemcel)

#### Background

Zynteglo (betibeglogene autotemcel) adds functional copies of a modified  $\beta$ -globin gene into patients' hematopoietic stem cells (HSCs) through transduction of autologous CD34+ cells with BB305 LVV. After Zynteglo infusion, transduced CD34+ HSCs engraft in the bone marrow and differentiate to produce red blood cells (RBCs) containing biologically active  $\beta^{A-T87Q}$ -globin (a modified  $\beta$ -globin protein) that will combine with  $\alpha$ -globin to produce functional adult hemoglobin (Hb) containing  $\beta^{A-T87Q}$ -globin (Hb<sup>AT87Q</sup>).  $\beta^{A-T87Q}$ -globin expression is designed to correct the  $\beta/\alpha$ -globin imbalance in erythroid cells of patients with  $\beta$ -thalassemia and has the potential to increase functional adult HbA and total Hb to normal levels and eliminate dependence on regular packed RBC transfusions (1).

#### Regulatory Status

FDA-approved indication: Zynteglo is an autologous hematopoietic stem cell-based gene therapy indicated for the treatment of adult and pediatric patients with  $\beta$ -thalassemia who require regular red blood cell (RBC) transfusions (1).

Zynteglo is for autologous use only and for one-time single-dose intravenous use only (1).

Patients are required to undergo HSC mobilization followed by apheresis to obtain CD34+ cells for product manufacturing. It is recommended that patients be maintained at a Hb  $\geq 11$  g/dL for at least 30 days prior to mobilization and 30 days prior to myeloablative conditioning.

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Granulocyte-colony stimulating factor (G-CSF) and plerixafor were used for mobilization and busulfan was used for myeloablative conditioning (1).

Screening for hepatitis B virus (HBV), hepatitis C virus (HCV), human T-lymphotrophic virus 1 and 2 (HTLV-1/HTLV-2), and human immunodeficiency virus 1 and 2 (HIV-1/HIV-2) should be performed in accordance with clinical guidelines before collection of cells for manufacturing (1).

Full myeloablative conditioning must be administered before infusion of Zynteglo. After completion of the myeloablative conditioning, a minimum of 48 hours washout should be allowed before Zynteglo infusion (1).

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**Related policies**

Exjade Jadenu, Feriprox

**Policy**

*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.*

Zynteglo may be considered **medically necessary** if the conditions indicated below are met.

Zynteglo may be considered **investigational** for all other indications.

## Prior-Approval Requirements

### Diagnosis

Patient must have the following:

Beta-thalassemia

**AND ALL** of the following:

- a. Beta-thalassemia diagnosis has been confirmed by globin gene testing
- b. Patient requires regular peripheral blood transfusions to maintain target hemoglobin levels
- c. Patient has **ONE** of the following:
  - i. Documented history of receiving transfusions of  $\geq 100$  mL per kilogram of body weight of packed red cells per year
  - ii. Disease had been managed under standard thalassemia guidelines

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- with  $\geq 8$  transfusions per year in the previous 2 years
- d. **NO** evidence of severe iron overload (e.g., T2\*-weighted magnetic resonance imaging measurement of myocardial iron of less than 10 msec)
  - e. Patient meets institutional requirements for a stem cell transplant procedure including **ALL** of the following:
    - i. Adequate Karnofsky performance status or Lansky performance status
    - ii. Absence of advanced liver disease
    - iii. Adequate estimated glomerular filtration rate (eGFR)
    - iv. Adequate diffusing capacity of the lungs for carbon monoxide (DLCO)
    - v. Adequate left ventricular ejection fraction (LVEF)
    - vi. Absence of clinically significant active infection(s)

**AND NONE** of the following:

- a. History of receiving prior gene therapy for beta-thalassemia or allogeneic hematopoietic stem cell transplant

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### Prior – Approval *Renewal* Requirements

None

#### Policy Guidelines

### Pre - PA Allowance

None

### Prior - Approval Limits

**Quantity** One infusion (only one PA approval for one infusion per lifetime)

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### Prior – Approval *Renewal* Limits

None

#### Rationale

#### Summary

Zynteglo is an autologous hematopoietic stem cell-based gene therapy. It is for one-time single-dose intravenous use only and is indicated for the treatment of adult and pediatric patients with  $\beta$ -thalassemia who require regular red blood cell (RBC) transfusions. Patients are required to

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undergo HSC mobilization following apheresis to obtain CD34+ cells for Zynteglo manufacturing. Full myeloablative conditioning must be administered before infusion of Zynteglo (1).

Prior authorization is required to ensure the safe, clinically appropriate, and cost-effective use of Zynteglo while maintaining optimal therapeutic outcomes.

### References

1. Zynteglo [package insert]. Somerville, MA: Bluebird Bio, Inc.; August 2022.

### Policy History

| Date           | Action/Reason                                                                                                                                                                                                                                                                         |
|----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| September 2022 | Addition to PA                                                                                                                                                                                                                                                                        |
| October 2022   | Per FEP: revised wording of leukocyte donor criterion to "Availability of human leukocyte antigen-identical or human leukocyte antigen-matched donor"                                                                                                                                 |
| December 2022  | Annual review                                                                                                                                                                                                                                                                         |
| December 2023  | Annual review                                                                                                                                                                                                                                                                         |
| April 2024     | Aligned with BCBSA policy: Re-organized requirements for clarity and organized requirements regarding performance status, eGFR, liver disease, cardiac function, lung function and infection status under a requirement to meet institutional requirements for a stem cell transplant |
| June 2024      | Annual review                                                                                                                                                                                                                                                                         |
| June 2025      | Annual review                                                                                                                                                                                                                                                                         |
| June 2026      | Annual review                                                                                                                                                                                                                                                                         |

### Keywords

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**This policy was approved by the FEP® Pharmacy and Medical Policy Committee on June 11, 2026 and is effective on July 1, 2026.**